

POSITION PAPER

# The EAACI/GA<sup>2</sup>LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update

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## Keywords

angioedema; consensus; hives; urticaria; wheal.

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## Abstract

This guideline is the result of a systematic literature review using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology and a structured consensus conference held on 28 and 29 November 2012, in Berlin. It is a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) with the participation of delegates of 21 national and international societies. Urticaria is a frequent, mast cell-driven disease, presenting with wheals, angioedema, or both. The life-time prevalence for acute urticaria is approximately 20%. Chronic spontaneous urticaria and other chronic forms of urticaria do not only cause a decrease in quality of life, but also affect performance at work and school and, as such, are members of the group of severe allergic diseases. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors and pathomecha-

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nisms. In addition, it outlines evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

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The wide diversity and number of different urticaria subtypes that have been identified reflect, at least in part, our increasing understanding of the causes and eliciting factors of urticaria and the molecular and cellular mechanisms involved in its pathogenesis. The aim of this guideline is to provide an updated definition and classification of urticaria, thereby facilitating the interpretation of divergent data from different centers regarding underlying causes, eliciting factors, and therapeutic responsiveness of subtypes of urticaria. Furthermore, this guideline provides recommendations for diagnostic and therapeutic approaches in common subtypes of urticaria. This guideline has involved societies and experts from all areas of the world and as a global guideline thus also takes into consideration that causative factors in patients, medical systems, and access to diagnosis and treatment vary in different countries.

## Methods

The detailed methods used in the development of this guideline 2013 revision and update, including all evaluations of the literature, are published in a separate paper for the sake of brevity and readability. A brief summary is provided here as Appendix 2.

In short, as members of the panel and delegates of their societies, the authors had prepared in advance their suggestions regarding the definition, classification, diagnosis, and treatment of urticaria. The resulting draft of the guideline took into account all available evidence in the literature (including Medline and Embase searches as well as manual search of abstracts at international allergy congresses between 2004 and 2012) and was based on the existing consensus papers of the first three symposia in 2000, 2004, and 2008 (1–6). These suggestions were then discussed in detail between the panel and the participants of the meeting. A consensus was finally achieved during a structured consensus conference using a TED voting system. The participation of urticaria specialists from 39 countries ensured that this consensus includes regional differences worldwide in viewpoint and provides a basis for improved comparison of future studies in the field of urticaria.

In the previous version of the guideline, studies were already partly evaluated using the GRADE approach. The key principle of the GRADE approach is to provide transparency and clear, explicit criteria for assessing the quality of evidence (see Table 1) and grading the strength of recommendations (7–11) based on risk *vs* benefits.

The following translation to the GRADE quality of evidence was used acknowledging that a more detailed assessment will possibly change the quality of evidence and that additional quality criteria are considered in GRADE.

SIGN level of evidence	GRADE quality of evidence
1 <sup>++</sup>	High
1 <sup>+</sup>	Moderate
1 <sup>−</sup>	Low
2 <sup>++</sup>	Low
2 <sup>+</sup>	Low
2 <sup>−</sup>	Very low
3	Very low
4	Very low

For this 2013 revision and update, a modified version of GRADE was applied throughout the guideline. The questions addressed were developed by the panel members and selected with respect to their relevance by all the panel members in a Delphi voting. The selection and wording process used as well as other methodological details are described in a separate

**Table 1** Levels of evidence for identified literature sources

The quality of the evidence was assessed using the Methodology Checklist 2: RCTs of the Scottish Intercollegiate Guidelines Network (SIGN; compare for (2))	
1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 <sup>−</sup>	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2 <sup>++</sup>	High-quality systematic reviews of case-controlled or cohort or studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2 <sup>+</sup>	Well-conducted case-controlled or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2 <sup>−</sup>	Case-controlled or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytic studies, for example case reports, case series
4	Expert opinion

RCT, randomized controlled trials.

report on methods used for the generation of this revision and update of the guideline. Briefly, the strength of a recommendation and the quality of supporting evidence were assessed independently by two assessors for each recommendation. They took into consideration as negative/risk: side-effects (graded on severity) and costs; and as benefits: reduction in urticaria symptoms (e.g., UAS7 [UAS, Urticaria Activity Score; UAS7, Average Urticaria Activity Score for 7 days] in newer studies) and improvement in quality of life (QoL). Importantly, the GRADE system permits strong recommendations supported by low- or (very rarely) very-low-quality evidence from downgraded RCTs or observational studies. On the other hand, weak recommendations may be based on high-quality evidence if other factors are important, for example the price of a treatment option.

The expression 'we recommend' was used for strong recommendations and 'we suggest' for weak recommendations in order to adhere to the same methodology used for the Allergic Rhinitis and its Impact on Asthma guideline 2008 update (10). This same terminology has also been adhered to in those parts of the guideline where the assessment of the evidence was not done in full.

Participants of the consensus conference were presented with a draft version of this document and were asked to discuss and vote whether they agreed with recommendations and other specific parts of the text. It was only allowed to vote yes or no, to ensure clear majority decisions. In statements not receiving votes >90% during the first voting, the recommendation was re-discussed, rephrased, and re-voted and passed in the following votings if a minimum of >75% agreement was achieved.

Conflicts of interest of all group members were collected prior to the consensus conferences. They were assessed by the steering committee. All declarations of conflicts of interest are presented as online Supporting Information to this guideline and in detail in the methods report.

## Definition

Urticaria is a disease characterized by the development of wheals (hives), angioedema, or both. Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur as a symptom, for example skin prick test, anaphylaxis, auto-inflammatory syndromes, or hereditary angioedema (bradykinin-mediated angioedema).

### *Clinical appearance*

Urticaria is characterized by the sudden appearance of wheals, angioedema, or both.

A wheal consists of three typical features:

- 1 It is characterized by a central swelling of variable size, almost invariably surrounded by a reflex erythema.
- 2 It is associated with itching or sometimes a burning sensation.
- 3 It has a fleeting nature, with the skin returning to its normal appearance, usually within 1–24 h. Sometimes wheals resolve even more quickly.

Angioedema is characterized by

- 1 A sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes and
- 2 Sometimes pain rather than itching and frequent involvement below mucous membranes. Its resolution is slower than that for wheals and can take up to 72 h.

### *Pathophysiological aspects*

Urticaria is a mast-cell-driven disease. Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated mast cells, result in sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment to urticarial lesions. The mast-cell-activating signals in urticaria are ill-defined and likely to be heterogeneous and diverse. Histologically, wheals are characterized by edema of the upper and mid-dermis, with dilatation of the postcapillary venules and lymphatic vessels of the upper dermis. In angioedema, similar changes occur primarily in the lower dermis and the subcutis. Skin affected by wheals virtually always exhibits upregulation of endothelial cell adhesion molecules and a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils and/or eosinophils, macrophages, and T cells, but without vessel-wall necrosis, which is a hallmark at *urticaria vasculitis* (12–14). A mild-to-moderate increase of mast cell numbers has also been reported by some authors. In delayed pressure urticaria, the infiltrate is typically located in the mid- to lower dermis. In some subtypes of urticaria, up-regulation of adhesion molecules (15) and altered cytokine expression are also seen in uninvolved skin (16). These findings underline the complex nature of the pathogenesis of urticaria, which has many features in addition to the release of histamine from dermal mast cells (17, 18).

These changes are also seen in a wide variety of inflammatory reactions and are thus not specific or of diagnostic value. A search for more specific histological biomarkers for different subtypes of urticaria is desirable.

## Considerations about patient-related outcomes in patients with urticaria

### *Quality of life*

Patient-related outcomes are important to be looked at in the treatment for urticaria (19). The available data indicate that urticaria has a detrimental effect on both objective functioning and subjective well-being. For example, O'Donnell et al. (20) showed that health status scores in patients with chronic spontaneous urticaria (CSU) are comparable to those reported by patients with coronary artery disease. Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in healthy subjects and in patients with respiratory allergy (21). A study of Poon et al. (22) focused on the extent and nature of disability in different types of urticaria, showing a large variation in Health-Related Quality of Life (HR-QoL) scores within different urticarial subsets. In this study, the assessment of HR-QoL was performed using generic tools.

A QoL Questionnaire specifically developed for CSU was validated, including physical, emotional, social, and practical

aspects characteristic of this condition (23). This new tool named Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) was originally generated and tested in the Italian language following well-established procedures. The CU-Q2oL meets the standards for validity with good construct validity, internal consistency, reliability, and responsiveness. These psychometric characteristics make it suitable for the assessment of the health burden of CSU. It has now been translated and validated in German, Spanish, Polish, Turkish, Greek, Bulgarian, Brazilian-Portuguese, and other versions are currently being validated (24–28). In addition, another questionnaire covers patients with angioedema (29). The Angioedema Quality of Life Questionnaire (AE-QoL), a symptom-specific QoL instrument, has been developed in German (29) and has been translated in various languages, including English (USA), Spanish, French, Azeri, Swedish, Hungarian, Romanian, Greek, and Polish.

### Which instrument should be used to measure QoL in urticaria?

We recommend using the validated CU-Q2oL and AE-QoL instruments for assessing QoL impairment and to monitor disease activity (strong recommendation/clinical consensus).

### Classification of urticaria on the basis of its duration, frequency, and causes

The spectrum of clinical manifestations of different urticaria subtypes is very wide. Additionally, two or more different subtypes of urticaria can coexist in any given patient.

Acute urticaria is defined as the occurrence of spontaneous wheals, angioedema, or both for <6 weeks. Table 2 presents a classification for clinical use of chronic urticaria subtypes. This revised classification deals with previous inconsistencies, for example physical urticarias may also be chronic

**Table 2** Classification of chronic urticaria subtypes (presenting with wheals, angioedema, or both)

Chronic urticaria subtypes	
Chronic spontaneous urticaria	Inducible urticaria
Spontaneous appearance of wheals, angioedema, or both $\geq 6$ weeks due to known or unknown causes	Symptomatic dermographism* Cold urticaria† Delayed pressure urticaria‡ Solar urticaria Heat urticaria§ Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

\*also called *urticaria factitia*, dermographic urticaria; †also called cold contact urticaria; ‡also called pressure urticaria; §also called heat contact urticaria.

conditions, but they were grouped separately due to the special nature of their eliciting physical factors. *Urticaria pigmentosa* (cutaneous mastocytosis), *urticaria vasculitis*, auto-inflammatory syndromes (e.g., cryopyrin-associated periodic syndromes or Schnitzler's syndrome), and nonmast cell mediators mediated/induced angioedema (e.g., bradykinin-mediated angioedema) are not considered to be subtypes of urticaria, due to their distinctly different pathomechanisms, but are listed in Table 3 for reference. Wheals are also features of several syndromes (Table 3).

### Assessment of disease activity and impact

Disease activity in spontaneous urticaria should be assessed both in clinical care and in trials with the UAS7 (Table 4), a unified and simple scoring system that was proposed in the last version of the guidelines and has been validated (30). The signs and symptoms are evaluated by the patient making this score especially valuable. The use of the UAS facilitates com-

**Table 3** Diseases related to urticaria for historical reasons and syndromes that present with hives and/or angioedema

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (e.g., HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), that is, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), or neonatal onset multisystem inflammatory disease (NOMID).
- Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
- Gleich's syndrome (episodic angioedema with eosinophilia)
- Well's syndrome (Granulomatous dermatitis with eosinophilia)

These diseases and syndromes are related to urticaria (i) because they present with wheals, angioedema, or both and/or (ii) because of historical reasons.

**Table 4** The UAS7 for assessing disease activity in CSU

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6 for each day is summarized over one week (maximum 42).

parison of study results from different centers. The UAS is based on the assessment of key urticaria symptoms (wheals and pruritus). It is suitable for the evaluation of disease activity by urticaria patients and their treating physicians. Furthermore, this scoring system has been widely used in trials and should thus be maintained for future comparison. As urticaria symptoms change frequently in intensity, the overall disease activity is best measured by advising patients to document 24-h self-evaluation scores once daily for several days. A modification of the UAS7 assessing signs and symptoms two times per day was also validated (31), but voting preferred to use the classical UAS because (i) measuring only once daily for the last 24 h does give a bias in patients with primarily nocturnal symptoms only and (ii) it has been more widely used and it is important to use the same tool worldwide in trials to allow comparison. The UAS7, that is, the sum score of seven consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of patients with CSU, as well as in some cases of patients with inducible or physical urticaria as well. For patients with angioedema, a novel activity score, the Angioedema Activity Score has been developed and validated (29). In addition to disease activity, it is important to assess the impact of disease on QoL both in clinical practice and in trials.

In physical urticaria and in cholinergic urticaria, the threshold of the eliciting factor(s) should be determined to assess severity, for example critical temperature and stimulation time thresholds for cold provocation in cold urticaria. These thresholds allow both patients and treating physicians to evaluate disease activity and response to treatment.

#### **Should the current classification be maintained in urticaria?**

We recommend to use this updated version of the classification 2013 revision (strong recommendation/clinical consensus).

#### **Should the current activity score (UAS7) be maintained assessing severity in urticaria?**

We recommend to use the UAS7 to assess severity (strong recommendation/clinical consensus).

### **Diagnosis of urticaria**

In the last two decades, many advances have been made in identifying causes of different types and subtypes of urticaria, for example, in CSU reviewed in Refs (32–33). Among others, autoreactivity including autoimmunity mediated by functional autoantibodies directed against the IgE receptor, pseudo-allergy (nonallergic hypersensitivity reactions) to foods and drugs, and acute or chronic infections (e.g., *Helicobacter pylori* or *Anisakis simplex*) have been described (34–44) (Table 5). However, there are considerable variations in the frequency of underlying causes in the different studies. This also reflects regional differences in the world, for

example, different traditional diets and different prevalence of infections. Thus, it is important to remember that not all possible causative factors need to be investigated in all patients and the first step in diagnosis is a thorough history, taking the following questions into consideration:

- 1 Time of onset of disease
- 2 Frequency/duration of and provoking factors for wheals
- 3 Diurnal variation
- 4 Occurrence in relation to weekends, holidays, and foreign travel
- 5 Shape, size, and distribution of wheals
- 6 Associated angioedema
- 7 Associated subjective symptoms of lesions, for example itch, pain
- 8 Family and personal history regarding urticaria, atopy
- 9 Previous or current allergies, infections, internal diseases, or other possible causes
- 10 Psychosomatic and psychiatric diseases
- 11 Surgical implantations and events during surgery, for example after local anesthesia
- 12 Gastric/intestinal problems
- 13 Induction by physical agents or exercise
- 14 Use of drugs (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
- 15 Observed correlation to food
- 16 Relationship to the menstrual cycle
- 17 Smoking habits (especially use of perfumed tobacco products or cannabis)
- 18 Type of work
- 19 Hobbies
- 20 Stress (eustress and distress)
- 21 Quality of life related to urticaria and emotional impact
- 22 Previous therapy and response to therapy
- 23 Previous diagnostic procedures/results

The second step of the diagnosis is the physical examination of the patient. This should include a diagnostic provocation test including drug, food, and physical tests where it is indicated by history.

All subsequent diagnostic steps will depend very much on patient history and on the nature of the urticaria subtype, as summarized in Fig. 1 and Table 5.

#### **Should routine diagnostic measures be performed in acute urticaria?**

We recommend against any routine diagnostic measures in acute urticaria (strong recommendation/clinical consensus).

#### **Should routine diagnostic measures be performed in chronic spontaneous urticaria?**

We recommend for only very limited routine diagnostic measures in chronic spontaneous urticaria (strong recommendation/clinical consensus).



**Table 5** Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic program* (suggested based on history only) For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None†
	Chronic spontaneous urticaria	Differential blood count. ESR or CRP Omission of suspected drugs (e.g., NSAID)	Test for (in no preferred order): (i) infectious diseases (e.g., <i>Helicobacter pylori</i> ), (ii) type I allergy, (iii) functional autoantibodies, (iv) thyroid hormones and autoantibodies, (v) skin tests including physical tests, (vi) pseudoallergen-free diet for 3 weeks, (vii) tryptase‡, (viii) autologous serum skin test, and (ix) lesional skin biopsy
Inducible urticaria	Cold urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)	Differential blood count and ESR or CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test and threshold test	None
	Heat urticaria	Heat provocation and threshold test	None
	Solar urticaria	UV and visible light of different wavelengths and threshold test	Rule out other light-induced dermatoses
	Symptomatic dermographism	Elicit dermographism and threshold test (dermographometer)	Differential blood count, ESR or CRP
	Vibratory Angioedema	Test with, for example, vortex	None
	Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Cutaneous provocation test. Skin tests with immediate readings, for example prick test	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

\*Depending on suspected cause.

†Unless strongly suggested by patient history, for example allergy.

‡As indication of severe systemic disease.

#### Should extended diagnostic measures be performed in chronic spontaneous urticaria?

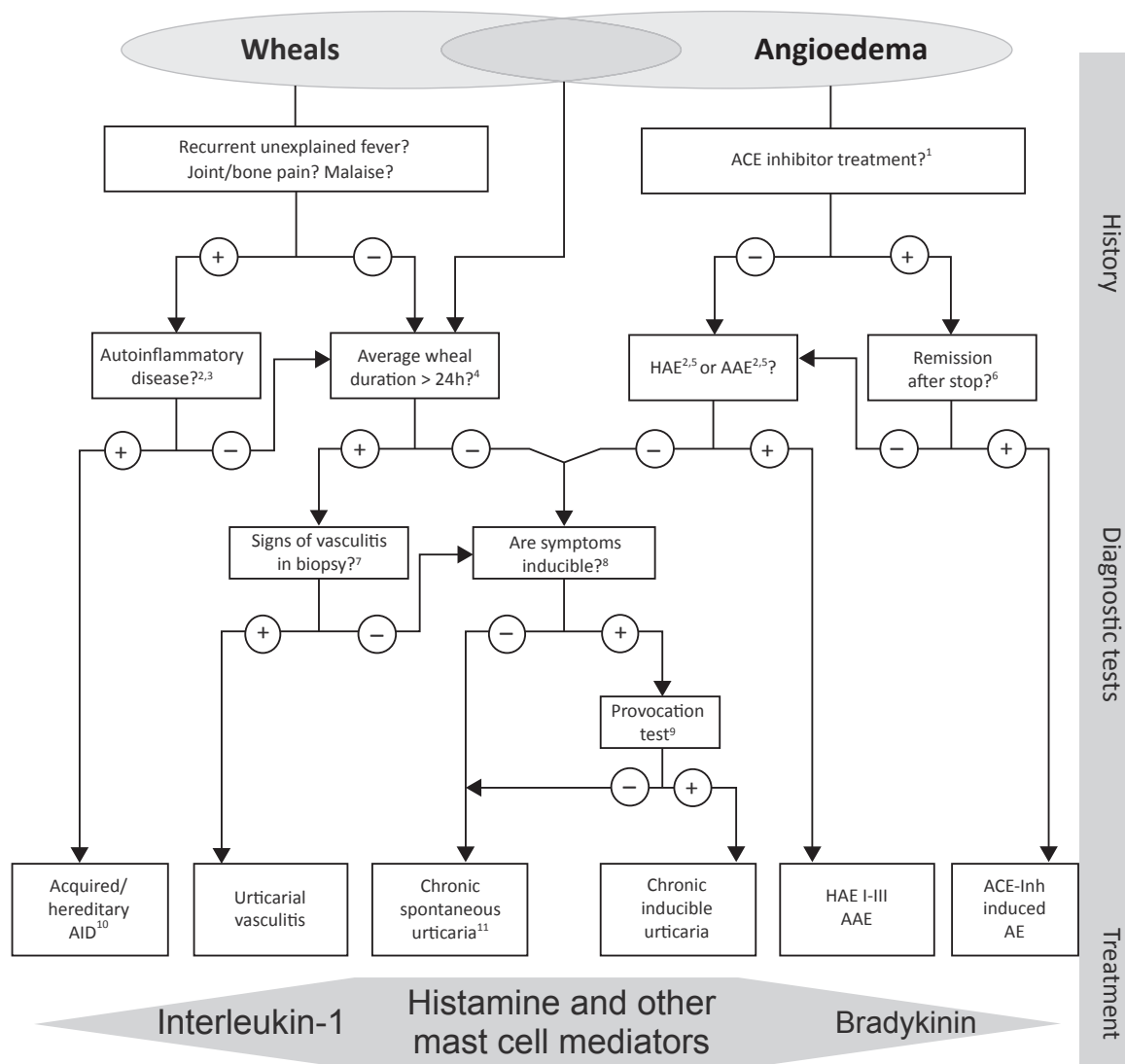
We recommend for only limited extended diagnostic measures in chronic spontaneous urticaria based on patient history (strong recommendation/clinical consensus).

#### Should routine diagnostic measures be performed in inducible, non-spontaneous subtypes of urticaria?

We recommend limiting routine diagnostic measures to determining the threshold of eliciting factors in inducible urticaria subtypes (strong recommendation/clinical consensus).

Intensive and costly general screening programs for causes of urticaria are strongly advised against. The following factors should only be investigated based on patient history. Type I allergy is a rare cause of CSU in patients who present with daily or almost daily symptoms, but may be considered in CSU patients with intermittent symptoms. In contrast, pseudo-allergic (non-allergic hypersensitivity reactions) to NSAIDs food or food additives may be more relevant for CSU with daily symptoms. Diagnosis should be based on an easy-to-follow diet protocol (see patient information page in different languages under <http://www.ecarf.org/>).

Bacterial, viral, parasitic, or fungal infections, for example, with *H. pylori*, *Streptococci*, *Staphylococci*, *Versinia*, *Giardia lamblia*, *Mycoplasma pneumoniae*, *Hepatitis virus*, *Norovirus*, *Parvovirus B19*, *Anisakis simplex*, *Entamoeba* ssp., *Blastocystis*



**Figure 1** Recommended diagnosis algorithm for urticaria. Diagnostic algorithm for patients presenting with wheals, angioedema, or both. AAE, Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh, angiotensin-converting enzyme inhibitor; AE, angioedema; AH, Antihistamine; AID, Auto-inflammatory disease; HAE, Hereditary angioedema; IL-1, Interleukin-1. <sup>1</sup>Other (new) drugs may also induce bradykinin-mediated angioedema. <sup>2</sup>Patients should be asked for a detailed family history and age of disease onset. <sup>3</sup>Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g., cryopyrin-associated periodic syndrome), if strongly suspected. <sup>4</sup>Patients should be asked: 'How long do your wheals last?' <sup>5</sup>Test for Complement C4, C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. <sup>6</sup>Wait for up to 6 months for remission; additional diagnostics to test for C1-inhibitor deficiency should only be performed, if the family history suggests hereditary angioe-

dema. <sup>7</sup>Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV (urticarial vasculitis)? <sup>8</sup>Patients should be asked: 'Can you make your wheals come?' <sup>9</sup>In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations (45) should be performed. <sup>10</sup>Acquired autoinflammatory syndromes (AIDs) include Schnitzler's syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary AIDs include cryopyrin-associated periodic syndromes (CAPS) such as familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS). <sup>11</sup>In some rare cases, recurrent angioedema is neither mast cell mediator-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as 'idiopathic angioedema' by some authors.

spp., have been implicated to be underlying causes of CSU. The frequency and relevance of infectious diseases varies between different patient groups and different geographical regions. For example, *Anisakis simplex*, a sea fish nematode, has only been discussed as a possible cause of recurrent acute spontaneous urticaria in areas of the world where uncooked fish is eaten frequently (46). The relevance of *H. pylori*, dental or ear, nose, and throat infections also appears to vary between patient groups. Altogether, more research is needed to make definitive recommendations regarding the role of infection in urticaria.

Routine screening for malignancies in the diagnosis of underlying causes for urticaria is not suggested. Although it is noted that a slightly increased prevalence has been reported in Taiwan (47), there is not sufficient evidence available for a causal correlation of urticaria with neoplastic diseases. Ruling out malignancies is, however, warranted if patient history (e.g., sudden loss of weight) points at this.

Currently, the only generally available test to screen for autoantibodies against either IgE or FcεR1 (the high affinity receptor) is the autologous serum skin test (ASST), a nonspecific screening test that evaluates the presence of serum histamine-releasing factors of any type, not just histamine-releasing autoantibodies. In some countries, a basophil release test is available and may be used. General experience, including that of the panel, is that healthy controls and patients without CSU do not have positive ASST responses as defined by an inflammatory red wheal response (48–60). In contrast to most previously published studies, some studies have demonstrated a relatively high prevalence of positive ASST reactivity in 30–50% of adult patients with allergic or nonallergic respiratory symptoms, reaching up to 80% in childhood populations (53–56, 61). In two of these studies, 40–45% of healthy individuals also had a positive ASST although the criteria that used to define positivity were adopted from those that had been validated only for CSU. The meaning of these discrepancies is unclear. The ASST should be performed with utmost care because infections might be transmitted if, by mistake, patients were injected with someone else's serum. A more refined laboratory test evaluates the *in vitro* histamine release from basophils. The subject is further elucidated in a separate EAACI/GA<sup>2</sup>LEN position paper (62).

Additional blood tests such as antinuclear antibody test can also be considered if the patient history points at this. Recent evidence has also shown an elevated D-dimer level in some CSU patients, those patients responded to anticoagulation therapy in an uncontrolled pilot study (63). This adds further information to older reports on anticoagulation as alternative treatment, but the overall relevance is not yet clear.

In physical urticaria, the routine diagnosis is mainly aimed at the identification of the subtype by the appropriate physical stimulation tests and to the determination of trigger thresholds. The latter is important as it allows for assessing disease severity and response to treatment. For most types of physical urticaria, no validated tools for provocation testing exist. Exceptions include cold urticaria, where a Peltier element-

based provocation device (TempTest<sup>®</sup>) is available (64, 65), symptomatic dermographism for which a dermographometers have been developed (66) and delayed pressure urticaria (67). In other physical urticarias or cholinergic urticaria, graded provocation tests with office-based methods, for example ergometer provocation in cholinergic urticaria, should be standardized in the single practice setting to allow comparison of disease activity at different time points in the same patient. Finally, contact urticaria should be demonstrated with cutaneous provocation tests, for example prick tests (68).

In some subjects with active CSU, several groups have noted blood basopenia and that blood basophils exhibit suppressed IgE-receptor-mediated histamine release to anti-IgE. Blood basophils are detected in skin lesions and in nonlesional skin of CSU patients. CSU remission is associated with increases in blood basophil numbers and IgE receptor triggered histamine response (69, 70). This finding, however, needs to be examined in future research and currently does not lead to diagnostic recommendations. However, it should be noted that a low basophil blood count should not result in further diagnostic procedures.

### Diagnosis in children

Urticaria can occur in all age groups. Acute spontaneous urticaria is common in infants and young children, particularly in atopics. For example, it was experienced by 42% of the placebo-treated children in the 18-month EPAAC study. Inducers included acute viral infection or (more frequently than in older children and adults) ingestion of food such as milk, egg, or peanut, to which the infant/child is sensitized. In these young patients, food-induced generalized acute urticaria is often a harbinger of anaphylaxis. They should therefore be investigated for sensitization to foods suggested by the history, in order to confirm their specific food trigger and, through avoidance of this trigger, prevent subsequent episodes.

The underlying causes of CSU appear not to be different between children and adults. In general, further epidemiological studies in children are needed. However, it is becoming apparent that the differences between the underlying causes of urticaria in children and adults are only small, indicating that the diagnostic approach should therefore be the same as in adults (71–73) except possibly in infants (74). However, there appear to be differences in the frequency of some of the underlying causes (75).

### Management of urticaria

#### Basic considerations

- 1 Urticaria is defined as a (with the exception of acute urticaria) chronic condition where partly unknown stimuli cause mast cells to release their mediators leading to small (wheals) or larger and deeper (angioedema) edema of the skin. While the classification of different subtypes is important in view of the diagnostic approach, the therapeutic approach is universal and based on the same principles as in other mast-cell-dependent diseases in the field of allergy:



- (i) elimination/avoidance of the cause or trigger/stimulus,
  - (i) symptomatic pharmacological treatment by reducing mast cell mediator release and/or the effect of these mediators at the target organ, and (iii) inducing tolerance.
- 2 For mast cell-dependent diseases in the field of allergy and immunology (n.b. the field of allergy and immunology covers not only the directly IgE-dependent allergic reactions), the common feature is that the underlying condition itself is chronic. The severity of symptoms and the nature and magnitude of the stimulus or stimuli provoking or perpetuating symptoms vary from one patient to another. Thus, a patient with grass pollen or peanut allergy is asymptomatic when not in contact with the stimulus, and a cold urticaria patient can be asymptomatic in a warm climate, but they are not healthy. Management and treatment needs to take these variations into consideration. For urticaria treatment, as in other allergic or immunologic diseases, an algorithm is needed to both serve the majority of patients with easy-to-treat symptoms and those being more refractory to treatment. It also has to be considered that the need for treatment within this algorithm may vary over time (step up – step down). This is in line with considerations of severity in other areas of allergy and immunology (76, 77).
- 3 Acute urticaria differs from all other types as it is self-limited. Treatment is usually focused on symptomatic relief.

#### Should treatment aim at complete symptom control in urticaria?

We recommend aiming for complete symptom control in urticaria as safely as possible (strong recommendation/clinical consensus following the WHO constitution in conformity with the Charter of the United Nations).

#### Identification and elimination/avoidance of the stimulus

With the use of this therapeutic approach, an exact diagnosis is a basic prerequisite. Identifying the cause of urticaria is not, however, easily possible in most cases, for example infections may be a cause, aggravating factor or unassociated bystander.

If remission following elimination of the suspected agent occurs, only recurrence of symptoms in a double-blind provocation test will provide definitive proof of its causative nature because spontaneous remission of urticaria might also occur incidentally in parallel with, but not because of, the elimination of a suspected cause or trigger.

**Drugs.** When such agents are suspected in the course of diagnosis, they should be omitted entirely or substituted by another class of agents if indispensable. Drugs causing non-allergic hypersensitivity reactions (the prototypes being NSAID) cannot only elicit, but can also aggravate pre-existing CSU (78), so that elimination in the latter case will only improve symptoms in some patients.

**Physical stimuli.** Avoidance of physical stimuli for the treatment of physical urticaria is desirable, but not always simple. Detailed information about the physical properties of the respective stimulus should make the patient sufficiently knowledgeable to recognize and control exposure in normal daily life. Thus, for instance, it is important in delayed pressure urticaria/angioedema and in symptomatic dermatographism/urticaria factitia to point out that pressure is defined as force per area and that simple measures, such as broadening of the handle of heavy bags for pressure urticaria or reducing friction in case of symptomatic dermatographism/urticaria factitia, may already be helpful in the prevention of symptoms. Similar considerations hold for cold urticaria where the impact of the chill factor in cold winds needs to be remembered. For solar urticaria, the exact identification of the range of eliciting wavelengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with an UV-A filter. However, in many patients, the threshold for the relevant physical trigger is low and total avoidance of symptoms is virtually impossible. Severe dermatographic urticaria is sometimes confused with CSU because seemingly spontaneous hives are observed where even loose-fitting clothing rubs on the patient's skin or unintentional scratching by patients readily develop wheals on that area.

**Eradication of infectious agents and treatment of inflammatory processes.** In contrast to physical urticaria where co-existing, potentially disease-sustaining factors are only found occasionally in cold and dermatographic urticaria (symptomatic dermatographism/urticaria factitia), CSU is often reported to be associated with a variety of inflammatory or infectious diseases. This is regarded as significant in some instances, but some studies show conflicting results and have methodological weaknesses. These infections, which should be treated appropriately, include those of the gastrointestinal tract, such as *H. pylori* (even if association with urticaria is not clear in the individual patient and a meta-analysis shows overall low evidence for this therapy (79), *H. pylori* should be eliminated as it is associated with gastric cancer) or bacterial infections of the nasopharynx (41, 80–83). Bowel parasites, a rare possible cause of CSU in developed industrial countries, should be eliminated (84). In the past, intestinal candidiasis was regarded as a highly important underlying cause of CSU (85), but more recent findings fail to support a significant causative role. Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as potentially causative for CSU in the recent past. This holds particularly for gastritis, reflux oesophagitis, or inflammation of the bile duct or gall bladder (37, 86). However, similar to infections, it is not easily possible to discern whether any of these are relevant causes of CSU.

**Reduction of functional autoantibodies.** There is still only little experience in the treatment for CSU by direct reduction of functional autoantibodies by plasmapheresis, which has been shown to be of temporary benefit in individual, severely affected patients (87). Due to high costs, this therapy is

suggested for autoantibody-positive CSU patients who are unresponsive to all other forms of treatment.

**Dietary management.** IgE-mediated food allergy is rarely the underlying cause of CSU (36, 37). If identified, the specific food allergens need to be omitted as far as possible. In a subgroup of CSU patients, pseudoallergic reactions (non-IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been observed (36, 37, 88–90). Since the last version of the guidelines, the proposed pseudoallergen-free diet has now also been successfully tested in different countries (91).

Similar to drugs, pseudoallergens can both elicit and aggravate CSU (92). In these cases, a diet containing only low levels of natural as well as artificial food pseudoallergens should be instituted and maintained for a prolonged period, at least 3–6 months. It should be underlined that avoidance of type I-allergens clears urticaria symptoms within 24–48 h if the relevant allergens are eliminated rapidly, whereas in pseudoallergy, a diet must often be maintained for a minimum of 3 weeks before beneficial effects are observed. Detailed information about dietary control can be found in the referenced articles. However, it should be pointed out that success rates may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effect of foodstuffs in causing urticaria, particularly in areas where the daily diet is greatly different from the one in Western Europe.

**Should patients with an allergic sensitization (positive specific IgE/skin prick test) avoid certain food items?**

We recommend that patients with a known sensitization based on specific IgE to food should only avoid these food items if there is relevant information e.g. double blind oral provocation test or a clear history, to prove that the sensitization has a clinical relevance for urticaria (strong recommendation/high level of evidence).

**Are pseudoallergen-free diets useful in the extended diagnostic program of chronic spontaneous urticaria?**

We recommend the use of pseudoallergen (non-allergic-hypersensitivity reaction agents) free diets in the extended diagnostic program of chronic spontaneous urticaria in patients with daily or almost daily symptoms only (strong recommendation/high-quality evidence).

*Inducing tolerance*

Inducing tolerance can be useful in some subtypes of urticaria. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where even a rush therapy with UV-A has

been proven to be effective within 3 days (93). However, tolerance induction is only lasting for a few days; thus, a consistent daily exposure to the stimulus just at threshold level is required which, for example, in case of cold baths is often not accepted by patients.

*Symptomatic pharmacological treatment*

The main option in therapies, however, aimed at symptomatic relief is to reduce the effect of mast cell mediators such as histamine, PAF, and others on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H1-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, continuous treatment with H1-antihistamines is of eminent importance in the treatment for urticaria (safety data are available for use of several years continuously). Continuous use of H1-antihistamines in chronic urticaria is supported not only by the results of clinical trials (94, 95) but also by the mechanism of action of these medications, that is, that they are inverse agonists with preferential affinity for the inactive state of the histamine H1-receptor and stabilize it in this conformation, shifting the equilibrium toward the inactive state.

However, in some cases, especially of CSU, other mast cell mediators (PAF, leukotrienes, cytokines) are also involved and a pronounced cellular infiltrate including basophils, lymphocytes, and eosinophils may be observed (96). These may respond completely to a brief burst of corticosteroid and may be relatively refractory to antihistamines.

Antihistamines have been available for the treatment of urticaria since the 1950s. However, the older first-generation antihistamines have pronounced anticholinergic effects and sedative actions on the central nervous system (CNS), which last longer than 12 h, whereas the antipruritic effects last only for 4–6 h. Consequently, many interactions have been described for these sedating antihistamines with alcohol and drugs affecting the CNS, such as analgesics, hypnotics, sedatives, and mood-elevating drugs. In addition, first-generation antihistamines can interfere with rapid eye movement sleep and impact on learning and performance. In the recent GA<sup>2</sup>LEN position paper (97), it is strongly recommended not to use first-generation antihistamines any longer in allergy both for adults and especially children. This view is shared by the WHO guideline Allergic Rhinitis and its Impact on Asthma (ARIA) (98). In this guideline, we thus recommend against the use of these sedating antihistamines for the routine management of chronic urticaria as first-line agents, except for the rare places worldwide in which modern second-generation antihistamines are not available. This recommendation is based on strong evidence regarding potential serious side-effects of old sedating antihistamines (lethal overdoses have been reported) and the availability of modern second-generation antihistamines worldwide at low costs, which not only lack these side-effects but also have a higher efficacy and duration of action. The side-effects of first-generation H1-antihistamines are most pronounced in promethazine, diphenhydramine, ketotifen, and chlorpheniramine and are well understood. They penetrate the blood–brain barrier,

bind to H1-receptors in the CNS, and interfere with the neurotransmitter effects of histamine. Positron-emission tomography studies document their penetration into the human brain and provide a new standard whereby CNS H1-receptor occupancy can be related directly to effects on CNS function (99). Impairment is particularly prominent during multitasking and performance of complex sensorimotor tasks such as driving.

Old first-generation H1-antihistamines are a particular concern in the elderly in whom they increase the risk of impaired cognition, inattention, disorganized speech, altered consciousness, and falls. The doses of drugs such as diphenhydramine, hydroxyzine, and doxepin, used in urticaria, are massive compared with the doses actually proven to be effective for the treatment of insomnia (i.e., to produce sedation), for example doxepin 3 mg.

The development of modern second-generation antihistamines led to drugs which are minimally or not sedating and free of anticholinergic effects. However, two of the earlier modern second-generation drugs, astemizole and terfenadine, which were essentially pro-drugs requiring hepatic metabolism to become fully active, had cardiotoxic effects if this metabolism was blocked by concomitant administration of ketoconazole or erythromycin. These two drugs are no longer available in most countries, and we recommend that they are not used.

Further progress with regard to drug safety was achieved by the development of the newer modern second-generation antihistamines cetirizine (metabolite of hydroxyzine), loratadine, and fexofenadine, some of which are mostly nonsedating metabolites of earlier sedative antihistamines. More recently, acrivastine, azelastine, bepotastine, bilastine, desloratadine, the active metabolite of loratadine, ebastine, epinastine, levocetirizine, the active enantiomer of cetirizine, mequitazine, mizolastine, olopatadine, and rupatadine (99) have been added to the list of modern second-generation antihistamines. Many of these antihistamines have not been appropriately studied in urticaria, and there are considerable clinical differences between them. Only seven of them (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine, and bilastine) have been tested in detail in urticaria. Taken together, modern second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile. However, up to date, well-designed clinical trials comparing the efficacy and safety of modern second-generation H1-antihistamines in CSU are largely lacking.

**Are modern second generation H1-antihistamines to be preferred over first generation H1-antihistamines in treatment of urticaria?**

We recommend that modern second generation H1-antihistamines are to be preferred over first generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence).

**Are modern second generation H1-antihistamines first line treatment in urticaria and to be preferred against other licensed medication?**

We recommend that modern second generation H1-antihistamines are to be used as first line treatment of urticaria (strong recommendation/high level of evidence).

There are numerous studies showing the benefit of a higher dosage of antihistamines in individual patients (100–102) corroborating earlier studies which came to the same conclusion employing first-generation antihistamines (103, 104). This has been verified in studies using up to fourfold higher than recommended doses of bilastine, cetirizine, desloratadine, levocetirizine, fexofenadine, and rupatadine (100, 101, 105–107).

Furthermore, a recent study showed the benefit of using desloratadine and levocetirizine at doses up to fourfold higher than the recommended dose in the majority of patients (105).

In summary, these studies suggest that the majority of patients with urticaria not responding to single dose will profit from up-dosing of antihistamines. Modern second-generation antihistamines at licenced doses are first-line treatment in urticaria, and up dosing is second-line treatment (Fig. 2).

**Is an increase in the dose to fourfold of modern second generation H1-antihistamines useful as second line treatment and to be preferred over other treatments in urticaria?**

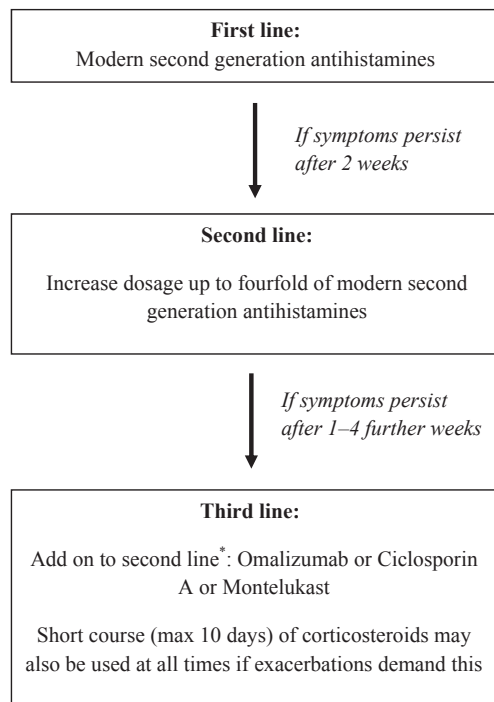
We recommend a trial of up to fourfold dose of modern second generation H1-antihistamines as second-line in the algorithm of treatment.

**Should modern second generation H1-antihistamines be taken regularly or as needed?**

We recommend modern second generation oral H1-antihistamines to be taken continuously in the lowest necessary dose rather than on demand (strong recommendation/high-quality evidence).

**Should different H1-antihistamines be used at the same time?**

We recommend preferably to updose modern second generation oral H1-antihistamines that do not cause sedation up to fourfold (strong recommendation/high-quality evidence) instead of combining different H1-antihistamines at the same time (strong recommendation/low-quality evidence).



**Figure 2** Recommended treatment algorithm for urticaria. \*The order of third-line treatments does not reflect preference. *First line* = *High-quality evidence*: Low cost and worldwide availability (e.g., modern second-generation antihistamines exist also in developing countries mostly cheaper than old sedating Antihistamines), per daily dose as the half-life time is much longer, very good safety profile, good efficacy. *Second line* = *high-quality evidence*: Low cost, good safety profile, good efficacy. *Third line as add-on to AH*. *Ciclosporin A* = *High-quality evidence*: Medium to high cost, moderate safety profile, good efficacy. *Omalizumab* = *High-quality evidence*: High cost, very good safety profile, very good efficacy. *Montelukast* = *Low quality evidence*: Low cost, good safety, low efficacy. *Short course of corticosteroids* = *Low quality evidence*: Low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but very low for lasting efficacy.

#### **If there is no improvement, should higher than fourfold doses of H1-antihistamines be used?**

We recommend to preferably updose modern second generation H1-antihistamines that do not cause sedation up to fourfold (strong recommendation/high-quality evidence) and to not further increase the dose.

#### **Further therapeutic possibilities for antihistamines refractory patients**

Omalizumab (anti-IgE) has now been shown to be very effective in the treatment for CSU, both in case reports and case series as well as in double-blind placebo-controlled studies in

antihistamine refractory selected patients (108–118). Omalizumab has also been reported (case reports and small series) to be effective in cholinergic urticaria (119), cold urticaria (120), solar urticaria (121), heat urticaria (122), symptomatic dermographism (123), and delayed pressure urticaria (124). For an overview in inducible urticaria, see Metz et al (125). Omalizumab is effective already in doses from 150 to 300 mg per month, often independently from total serum IgE (126).

#### **Is omalizumab useful in the treatment of patients unresponsive to high doses of H1-antihistamines as third-line treatment?**

We recommend a trial of omalizumab as add on therapy to modern second generation H1-antihistamines as third-line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence).

Ciclosporin A also has a moderate, direct effect on mast cell mediator release (127, 128). Ciclosporin A has now been shown to be effective in double-blind placebo-controlled studies and is the only agent of this type to inhibit basophil histamine release. Efficacy of ciclosporin A in combination with a modern second-generation H1-antihistamine has been shown in placebo-controlled trials (129, 130) as well as open controlled trials (131), but this drug cannot be recommended as standard treatment due to a high incidence of adverse effects (130). It is recommended only for patients with severe disease refractory to any dose of antihistamine, but ciclosporin A has a far better risk/benefit ratio compared with long-term use of steroids.

#### **Is ciclosporin A useful as add on treatment in patients unresponsive to high doses of H1-antihistamines as third-line treatment?**

We recommend a trial of ciclosporin A as add on therapy to modern second generation H1-antihistamines as third-line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence).

Some older RCTs have assessed the use of antileukotrienes. Studies are difficult to compare due to different populations studied, for example, inclusion of only aspirin and food additive intolerant patients or exclusion of ASST-positive patients. In general, the level of evidence for the efficacy of leukotriene receptor antagonists in urticaria is low but best for montelukast.

#### **Should leukotriene antagonists be used in the third line treatment of urticaria?**

We suggest a trial of montelukast as add on therapy to modern second generation H1-antihistamines as third-line in the treatment of urticaria (weak recommendation/low level of evidence).



At present, topical corticosteroids are frequently successfully used in many allergic diseases, but in urticaria, topical steroids are not helpful (with the possible exception of pressure urticaria on soles as alternative therapy with low evidence). If systemic corticosteroids are used, doses between 20 and 50 mg/day are required with obligatory side-effects on long-term use. There is a strong recommendation against the long-term use of corticosteroids outside specialist clinics if it can be avoided. Depending on the country, it must be noted that steroids are also not licensed for chronic urticaria (e.g., in Germany prednisolone is only licenced for acute urticaria). For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids, that is, treatment of a maximum of up to 10 days, may, however, be helpful to reduce disease duration/activity (132, 133). Nevertheless, well-designed randomized clinical trials are lacking.

#### **Should oral corticosteroids be used in the treatment of urticaria?**

We recommend against the long-term use of systemic corticosteroids in urticaria (strong recommendation/high level of evidence).

and

We suggest a trial of a short course of systemic corticosteroids in urticaria as third-line therapy or as an option for acute exacerbation (weak recommendation/low level of evidence).

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in the majority of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. Before changing to an alternative therapy, it is recommended to wait for 1–4 weeks to allow full effectiveness.

As the severity of urticaria may fluctuate, and as spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months.

Except for omalizumab and ciclosporin A, which both have restrictions due to their high cost, many of the alternative methods of treatment, such as combinations of modern second-generation H1-antihistamines with antileukotrienes, are based on clinical trials with low levels of evidence (Table 5). Based on the level of evidence, the recommended third-line treatment options are thus limited (see algorithm Fig. 2).

For H-antagonists and dapsone, still recommended in the previous version of the guideline, the evidence is too low to maintain this as recommendable in the algorithm, but they may still have relevance as they are very affordable in some poorer healthcare systems. For sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, and intravenous immunoglobulins (IVIG) only trials of low quality or case series have been published (2) (Table 5).

Antagonists of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (134) and IVIG (135–138), which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (i.e., anti-TNF- $\alpha$  for delayed pressure urticaria and IVIG for CSU).

Phototherapy has been successfully used in mastocytosis and is helpful in treatment-resistant patients with this condition (139). For the treatment of CSU and symptomatic dermatographism, UV-A, PUVA, and UV-B (nb-UVB) treatment for 1–3 months can be added to antihistamine treatment (140–142).

On the other hand, some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo-controlled studies and should no longer be used in the average patient (although grade of recommendation is low). These include tranexamic acid and sodium cromoglicate in CSU (143, 144), nifedipine in symptomatic dermatographism/urticaria factitia (145), and colchicine and indomethacin in delayed pressure urticaria (146, 147). However, more research may be needed for patient subgroups, because recently (63) a pilot study of patients with elevated D-dimer levels showed that tranexamic acid therapy may be effective. This has been supported by other authors investigating anti-coagulants in urticaria as pointed out above.

#### **Treatment of special populations**

##### *Children*

Many clinicians use first-generation, sedating H1-antihistamines as their first choice in the treatment for children with allergies assuming that the safety profile of these drugs is better known than that of the modern second-generation H1-antihistamines due to a longer life on the market. Also, the use of modern second-generation H1-antihistamines is not licenced for use in children <6 months of age, while the recommendation for the first-generation H1-antihistamines is sometimes less clear because these drugs were licenced at a time when the code of 78 good clinical practice for the pharmaceutical industry was less stringent. As a consequence, many doctors choose first-generation antihistamines which, as pointed out above, have a lower safety profile compared with modern second-generation H1-antihistamines. A strong recommendation was made by the panel to discourage the use of first-generation antihistamines in infants and children. Thus, in children, the same first-line treatment and up-dosing (weight adjusted) is recommended as in adults. Only medications with proven efficacy and safety in the pediatric population should be used. Cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have been well studied in children, and their long-term safety has been well established in the pediatric population. In addition, the choice of the modern second-generation H1-antihistamine in children depends on the age and availabilities as not all are available as syrup or fast dissolving tablet suitable for children and the lowest licenced age also differs from country to country. All further steps should be based on individual considerations.

#### **Should the same treatment algorithm be used in children?**

We suggest the same treatment algorithm to be used in children with chronic urticaria (weak recommendation/clinical consensus).



*Pregnant and lactating women*

The same considerations in principle apply to pregnant and lactating women. On one hand, use of any systemic treatment should generally be avoided in pregnant women, especially in the first trimester. On the other hand, pregnant women have the right to best possible therapy. While the safety of treatment has not been systematically studied in pregnant women with urticaria, it should be pointed out that the possible negative effects of increased levels of histamine occurring in urticaria have also not been studied in pregnancy. Regarding treatment, no reports of birth defects in women having used modern second-generation antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine (148) and one large meta-analysis for loratadine (149). Furthermore, as several modern second-generation antihistamines are now prescription free and used widely in both allergic rhinitis and urticaria, it must be assumed that many women have used these drugs especially in the beginning of pregnancy, at least before the pregnancy was confirmed. Nevertheless, as the highest safety is mandatory in pregnancy, the suggestion for the use of modern second-generation antihistamines is to prefer loratadine with the possible extrapolation to desloratadine and cetirizine with a possible extrapolation to levocetirizine. All H1-antihistamines are excreted in breast milk in low concentrations. Use of second-generation H1-antihistamines is advised, as nursing infants occasionally develop sedation from the old first-generation H1-antihistamines transmitted in breast milk.

The increased dosage of modern second-generation antihistamines can only be carefully suggested in pregnancy because safety studies have not been carried out, and with loratadine, it must be remembered that this drug is metabo-

lized in the liver. First-generation agents may be cautiously employed when symptoms dictate in the face of nonresponse to modern second-generation antihistamines. Use of first-generation H1-antihistamines immediately before parturition may cause respiratory depression and other adverse effects in the neonate (the first-generation H1-antihistamines with the best safety track record in pregnancy are chlorpheniramine and diphenhydramine). All further steps should be based on individual considerations, with a preference for medications that have a satisfactory risk-to-benefit ratio in pregnant women and neonates with regard to teratogenicity and embryo toxicity. For example, cyclosporine, although not teratogenic, is embryo-toxic in animal models and is associated with preterm delivery and low birth weight in human infants (the median gestation duration of infants born to mothers taking cyclosporine is 35.7 weeks, and the median birth weight of their infants is 2.2 kg). Whether the benefits of cyclosporine in chronic urticaria are worth the risks in pregnant women will have to be determined on a case-by-case basis. However, all decisions should be reevaluated according to the current recommendations published by regulatory authorities.

#### Should the same treatment algorithm be used in pregnant women and during lactation?

We suggest the same treatment algorithm be used in pregnant women and during lactation in urticaria (weak recommendation/clinical consensus).

**Table 6** Areas of further research in urticaria

Global epidemiology, in adults and children
The socio-economic consequences
Identification of mast cell/basophil activating factors
Identification of new histological markers
Identification of serum biomarkers of urticarial activity/mast cell activation
Determination of minimal important differences for instruments that assess disease activity or impact relevant response (e.g., UAS, CU-Q2oL)
Clarification of the role of coagulation/coagulation factors in CSU
Development of commercially available <i>in vitro</i> tests for detecting serum auto-antibodies for anti-IgE or anti-FcεRI
Clarification of associated psychiatric/psychosomatic diseases and their impact
Pathomechanisms in antihistamine-resistant urticaria/angioedema
Double-blind control trials comparing different modern second-generation anti-H1s in higher doses in CSU and different subtypes of urticaria
Regular v. on demand use of anti-H1 antihistamines on the duration of urticaria/severity of urticaria
Multicenter studies on the possible effect of anticoagulants (oral and heparin derivatives) on CSU
Controlled multicenter trials on the possible effect of add-on of anti-H2, montelukast, sulfone, methotrexate, azathioprine

#### Need for further research

The panel and participants identified several areas in which further research is needed. These points are summarized in Table 6.

#### Acknowledgments

This guideline is the result of the formalized international process involving, in addition to the four founder societies, many societies and as such reflect an international compromise. National procedures as outlined by the individual participating societies in national guidelines may differ. However, while worldwide harmonization of treatment is only partly possible, a harmonization of nomenclature, classification, and management approaches is highly desirable. We thank the AAAAI for their input, review and thoughtful comments throughout the guidelines development process. Two English-speaking patients were present during the Urticaria Guideline meetings.

#### Conflicts of interest

A complete declaration of the authors' conflicts of interest is presented in the online version of this paper (see Supporting Information).

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Voting results.

**Data S2.** Physicians and specialists who contributed to the development of this revision and update of the guidelines by

active participation in the democratic process and discussion within the 4th International Consensus Meeting on Urticaria 2012.

**Data S3.** Conflicts of interest.

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## Appendix 1

### Societies involved in the Urticaria Guideline

AAAAI, American Academy of Allergy, Asthma & Immunology (see Acknowledgments); AEDV, Spanish Academy of Dermatology and Venereology; ASBAI, Brazilian Association of Allergy and Immunopathology; CDA, Chinese Dermatologist Association; CSACI, Canadian Society of Allergy and Clinical Immunology; DDG, German Society of Dermatology; DGAKI, German Society of Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESCD, European Society of Contact Dermatitis; GA<sup>2</sup>LEN, Global Allergy and Asthma European Network; IAACI, Israel Association of Allergy and Clinical Immunology; IADVL, Indian Association of Dermatologists, Venereologists and Leprologists; JDA, Japanese Dermatological Association; ÖGDV, Austrian Society for Dermatology; SDF, French Society of Dermatology; SGD, Swiss Society for Dermatology and Venereology; SPDV, Portuguese Society of Dermatology and Venereology; MSAI, Malaysian Society of Allergy and Immunology; UNEV, Urticaria Network; WAO, World Allergy Organization.

## Appendix 2

### Methods report on the development of the 2013 revision and update of the EAACI/GA<sup>2</sup>LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria

The methods report on the development of the updated international guideline on urticaria provides in-depth information on the development process of the 2013 revision of this international guideline. The update and revision of the guidelines was based on three previous versions of the guideline, which resulted from urticaria guideline consensus conferences in 2000, 2004 and 2008 (1–6). The guideline itself was developed in alignment with the quality criteria contained within the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, and the German Association of Scientific Medical Societies (AWMF).

The societies nominated a balanced number of experts representing the different societies, geographical regions and specialties in medicine involved in the treatment of urticaria, i.e. dermatologists, allergologists, pediatricians, pharmacologists and representatives of patients' organizations. The process was supervised by A. Nast, a methodologist in guideline

preparation with background knowledge as a dermatologist. Prior to the consensus meeting a list of questions was developed by the expert panel's steering committee for review and rating. The key questions were prepared with answers according to the available evidence by the expert panel.

The formalized literature research performed entailed:

- 1 The previous versions of the guideline (1–6). For the previous versions of the guideline a systematic search as described in the respective publications had been conducted and all randomized trials published up to and in 2008 had been evaluated and documented in GRADE tables.
- 2 A new literature search for all publications as of 2008. This literature research was based on the systematic research in Medline, Embase, Cochrane Library and Medline in Process. After checking for duplicates, all abstracts were screened by two independent researchers, 188 full texts were obtained and 67 were included in the body of evidence. The included literature was selected with respect to their hierarchy in the 'evidence pyramid', e.g. if a good systematic review was available and up to date no further systematic analysis of randomized controlled trials (RCTs) or cohort studies was done. This was chosen in case of existing high-quality RCTs, no further systematic analysis of cases series or case reports was done.

In the previous version of the guideline, studies were evaluated using the GRADE approach. The key principle of this approach is to provide transparency as well as clear and explicit criteria for assessing the quality of evidence and for grading the strength of recommendations (9) based on risks vs benefits. The strength of a recommendation and the quality of supporting evidence were assessed independently for each recommendation, taking into consideration negative and positive effects such as unwanted effects, reduction of urticaria symptoms, practicability, feasibility and costs. Importantly, the GRADE system permits strong recommendations supported by low- or, very rarely, very low-quality evidence from downgraded RCTs or observational studies. On the other hand, weak recommendations may be based on high-quality evidence if other factors are important, e.g. the price of a treatment option.

The phrase 'we recommend' was used for strong recommendations and 'we suggest' for weak recommendations in order to adhere to the same methodology used for the Allergic Rhinitis and its Impact on Asthma guideline 2008 update (10).

The consensus meeting was held in Berlin from 28 to 29 November 2012. Based on the prepared questions and the previous version of the guideline, a draft manuscript was

prepared for the consensus meeting which included the presence of more than 200 specialists from 39 countries from all over the world. All participants were equipped with printouts of the documents prepared. To ensure that the guideline recommendations are both evidence-based and practical, all of them were discussed and accepted by voting during the consensus meeting.

If a recommendation did not achieve 90% agreement in the first voting, the respective recommendation was then re-discussed and, if needed, rephrased. In order to pass the second voting round, a minimum of 75% agreement had to be achieved. After finishing the document the newly phrased guidelines were sent out for an extensive external review by all societies involved. This step was made specifically to ensure that possible national legislation would not contradict the guideline contents.

One of the societies originally involved in the preparation at this stage made the decision not to endorse the guideline

as it felt that there were too many discrepancies with already existing recommendations in their own country.

The methods report in extensive detail, displaying all of the different phrasings discussed during the meeting, will be available online (150). The validity of the guideline is four years (2017). Since new interventions may be licensed or relevant changes in information (for example, on adverse events) may become available before this point, the steering committee will evaluate the need for an earlier update of the whole guideline or individual questions at regular intervals.

In conclusion, the process of revision of the urticaria guideline is a good example allowing an advanced methodology for evidence-based medicine but also including a variety of opinions, not only of experts in the field who are mainly based in academic institutions, but also of specialists who are involved in daily routine practice in this field of treatment.